A STUDY TO EVALUATE THE CORRELATION BETWEEN SEROLOGICAL PROFILE AND HISTOPATHOLOGY OF LUPUS NEPHRITIS

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CERTIFICATE

This is to certify that the dissertation titled **"A STUDY TO EVALUATE THE CORRELATION BETWEEN SEROLOGICAL PROFILE AND HISTOPATHOLOGY OF LUPUS NEPHRITIS"** submitted by **Dr. C. VASUDEVAN** to the Faculty of Nephrology, The Tamilnadu Dr.MGR Medical University, Chennai in partial fulfillment of the requirement for the award of DM Degree in Nephrology branch is a bonafide work carried out by him under direct supervision and guidance.

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CONTENTS

ABBREVIATIONS

- ARA – American Rheumatism Association
- ANA – Antinuclear antibody
- APLA – Antiphospholipid antibody
- ANCA – Antinuclear cytoplasmic antibody
- ACEI – Angiotensin converting enzyme inhibitor
- ARB – Angiotensin II receptor blockers
- CNS – Central nervous system
- CIC – Circulating immune complex
- C3,C4 – Complement factors 3,4
- CTLA 4 - Cytotoxic T lymphocyte antigen 4
- DRVT – Dilute Russell viper venom test
- dsDNA – double stranded deoxy ribonucleic acid
- EBV – Epstein Barr virus
- ELISA – Enzyme linked immunosorbent assay
- EM – Electron microscopy
- GBM – Glomerular basement membrane
- GN – Glomerulonephritis
- HLA – Human leucocyte antigen
- HIV – Human immunodeficiency virus

- HBsAg – Hepatitis B surface antigen
- HCV – Hepatitis C virus
- IF – Immunofluorescence
- IFN – Interferon
- ISN/RPS – International society of nephrology/Renal pathology society
- LM – Light microscopy
- LN – Lupus nephritis
- LFT – Liver function test
- MMF – Mycophenolate mofetil
- NIH – National institute of health
- PGs – Prostaglandins
- RFT – Renal function test
- SLE – Systemic lupus erythematosus
- Sm – Smith
- TLR – Toll like receptor
- UV light – Ultra violet light
- USG - KUB – Ultrasonogram – Kidney ureter bladder
- WHO – World health organisation

INTRODUCTION

Systemic lupus erythematosus is an autoimmune disease of unknown etiology, characterized by the involvement of multiple organ systems [1]. Organ damage is mediated by tissue binding autoantibodies and immune complexes. The hallmark of SLE is the presence of serum autoantibodies directed to nuclear constituents (i.e., antinuclear antibodies, ANA). In most of the patients, these autoantibodies are present for a few years before the first clinical symptoms appear [2]. The clinical presentation and course of SLE are extremely variable. Some patients have spontaneous remissions; others may have mild musculoskeletal involvement which responds to therapy and a few die from progressive severe multisystem disease unresponsive to immunosuppressive therapy[2]. SLE commonly involves skin, joints, kidneys, serosal surfaces including pleura and pericardium, CNS and hematopoietic system.

Lupus nephritis is one of the common manifestations of SLE. Diagnosis of SLE is based on the 11 criteria defined by American Rheumatism Association (ARA). SLE patients develop wide range of autoantibodies [4,11,12,13]. ANA is the most sensitive test for SLE and is present in more than 90% of patients but not specific for SLE. Anti

dsDNA is a more specific but less sensitive marker of SLE. High titre of anti dsDNA correlates with disease activity and especially with lupus nephritis[3, 4, 12, 14]. Serum levels of complements C3 and C4 are usually decreased in active SLE and in active lupus nephritis [3, 4, 6, 7, 8, 9]. Most of the patients with active proliferative lupus nephritis have high titre of anti dsDNA and low C3 and C4 levels.

Nowadays renal biopsy is recommended in almost all patients who have clinical or laboratory evidence of renal involvement to determine the histological class of lupus nephritis and thereby to plan therapy. But the requirement of renal biopsy has not been studied scientifically so far. So this study aimed to look at the need for renal biopsy in lupus nephritis scientifically[90].

REVIEW OF LITERATURE

Lupus nephritis is a frequent and potentially life threatening complication of SLE [3,4,7,8,9,10]. Almost 50 to 60% of patients with SLE have clinically significant renal involvement at the time of diagnosis. The diagnosis of SLE can be established by the presence of certain clinical and laboratory criteria defined by American Rheumatism Association (ARA).

Diagnostic Criteria for Systemic Lupus Erythematosus	
Malar rash	Fixed erythema, flat or raised, over the malar eminences
Discoid rash	Erythematous circular raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur
Photosensitivity	Exposure to ultraviolet light causes rash
Oral ulcers	Includes oral and nasopharyngeal ulcers, observed by physician
Arthritis	Nonerosive arthritis of two or more peripheral joints, with tenderness, swelling, or effusion
Serositis	Pleuritis or pericarditis documented by ECG or rub or evidence of effusion
Renal disorder	Proteinuria >0.5 g/day or 3+ on dipstick , or cellular casts
Neurologic disorder	Seizures or psychosis without other causes

Hematologic disorder	Hemolytic anemia or leukopenia (<4000/μL) or lymphopenia (<1500/ μL) or thrombocytopenia(<100,000/ μL) in the absence of offending drugs
Immunologic disorder	Anti-dsDNA, anti-Sm, and/or anti-phospholipid antibodies
Antinuclear antibodies	An abnormal titer of ANA by immunofluorescence or an equivalent assay at any point in time in the absence of drugs known to induce ANAs

Any four of 11 criteria over a life time gives 96% sensitivity and specificity for SLE.

EPIDEMIOLOGY:

Women of child bearing age group between 15 and 45 years are more commonly affected. Female to male ratio is 10:1 [3, 4, 5, 6]. The gender predominance is less pronounced in children and elderly individuals. Incidence of renal disease is same in males and females. Lupus nephritis is more severe in children and males and is less likely in elderly individuals [5, 6, 8, 9]. The overall incidence of SLE ranges from 1.8 to 7.6 cases 1, 00,000 with a prevalence from 40 to 200 cases per 1, 00,000.

ETIOLOGY AND PATHOGENESIS OF SLE:

There is a complex interplay between genetic, environmental and hormonal factors with abnormal immune response results in autoimmunity in SLE.

Multiple genes predispose to SLE. This is supported by familial clustering of cases, concordance of SLE in identical twins (>25%) and the frequency of positive autoantibodies and autoimmune disorders in the family members of patients with SLE. Certain HLA genotypes (e.g., HLA B8, DR2 & DR3) and homogenous deficiency of certain complement factors, like C1q, C2, C4 and FCγR III polymorphisms carry a high risk of development of lupus [5,8,11]. Genome wide association studies identified 17 susceptible loci that involve genes associated with B cell signaling, Toll like receptors and neutrophil function [12].

Environmental factors like exposure to UV light (sun light), Epstein Barr virus, prolonged occupational exposure to silica dust and current smoking may also play a role in the onset of SLE[2]. UV light exposure can precipitate and exacerbate SLE and lupus nephritis possibly by increasing apoptosis in keratinocytes[5,8]. EBV antigens can mimic human antigen (antigen mimicry) and trigger SLE in susceptible individuals. Hormonal factors also play a role in SLE as evidenced by strong female preponderance and exacerbation of SLE with oestrogen containing oral

contraceptive pills and hormone replacement therapy. Estradiol binds to receptors in B & T lymphocytes, increasing activation and survival of these cells and thereby inducing prolonged immune responses and antibody production.

Abnormalities of immune regulation result in loss of self tolerance and subsequent autoimmune responses [4,5,6,15]. Defective autoregulation of T cells, abnormal exposure to self antigen, self antigen driven T cell hyperactivity and polyclonal proliferation of B Cells due to increased B cell stimulating cytokines may contribute to production of autoantibodies [4,13]. These autoantibodies are directed against nucleic acids, nucleosomes (DNA-histone complex), chromatin antigens and small nuclear and cytoplasmic ribonuclear proteins.

Autoantibodies in Systemic Lupus Erythematosus (SLE)			
Antibody	**Prevalence, %**	**Antigen Recognized**	**Clinical Utility**
Antinuclear antibodies	98	Multiple nuclear	Best screening test; repeated negative tests make SLE unlikely
Anti-dsDNA	70	DNA (double-stranded)	High titers are SLE-specific and in some patients correlate with disease activity, nephritis, vasculitis
Anti-Sm	25	Protein complexed to 6 species of nuclear U1 RNA	Specific for SLE; no definite clinical correlations; most patients also have anti-RNP; more common in blacks and Asians than whites
Anti-RNP	40	Protein complexed to U1 RNA	Not specific for SLE; high titers associated with syndromes that have overlap features of several rheumatic syndromes including SLE; more common in blacks than whites

Anti-Ro (SS-A)	30	Protein complexed to hY RNA, primarily 60 kDa and 52 kDa	Not specific for SLE; associated with sicca syndrome, predisposes to subacute cutaneous lupus, and to neonatal lupus with congenital heart block; associated with decreased risk for nephritis
Anti-La (SS-B)	10	47-kDa protein complexed to hY RNA	Usually associated with anti-Ro; associated with decreased risk for nephritis
Antihistone	70	Histones associated with DNA (in nucleosome, chromatin)	More frequent in drug-induced lupus than in SLE
Antiphospholipid	50	Phospholipids, β2glycoprotein 1 cofactor, prothrombin	Three tests available—ELISAs for cardiolipin and β2 glycoprotein 1, sensitive prothrombin time (DRVVT); predisposes to clotting, fetal loss, thrombocytopenia

Antierythrocyte	60	Erythrocyte membrane	Measured as direct Coombs' test; a small proportion develops overt hemolysis
Antiplatelet	30	Surface and altered cytoplasmic antigens on platelets	Associated with thrombocytopenia but sensitivity and specificity are not good; this is not a useful clinical test
Antineuronal (includes anti-glutamate receptor)	60	Neuronal and lymphocyte surface antigens	In some series a positive test in CSF correlates with active CNS lupus.
Antiribosomal P	20	Protein in ribosomes	In some series a positive test in serum correlates with depression or psychosis due to CNS lupus

Abnormal exposure to self antigen may occur through nuclear autoantigen clustering on the apoptotic blebs which may be associated with germ line mutation and leading on to expansion of autoreactive T cells. Spontaneous and inducible mouse animal models, like NZB B/W F1 hybrid, BxSB/yaa and MRL/lpr models showed that defective

apoptosis may lead to defective clonal deletion of T cells and induce B cell proliferation[8,11].

In SLE, some autoantibodies are directly pathogenic, e.g., antibodies causing autoimmune hemolytic anemia. Others combine with antigen to produce immune complexes which deposit in various organs if they are not adequately cleared from the circulation[8,22]. Usually the complement components help in the clearance of immune complexes, but they also get activated and incorporated into the immune complexes and contribute to the inflammatory cascade and irreversible organ damage.

PATHOGENESIS OF LUPUS NEPHRITIS:

In SLE, autoantibodies are produced against various antigens like dsDNA, Sm, RNA, Ro, La and histones[14,19]. Lupus nephritis has been considered as a human prototype of classical experimental immune complex mediated glomerulonephritis[20]. A hallmark of LN is the deposition of circulating immune complexes (CICs) and the in situ formation of others. Although the patients have autoantibodies against dsDNA, Sm antigen and C1q, the exact role of each antibody in the immune complex formation seen in glomerular disease remains unclear.

The chronic deposition of CICs plays a major role in the mesangial and endocapillary patterns of LN. Size, charge and avidity of immune complexes, local hemodynamic factors and the clearing ability of the mesangium all influence the localization of CICs within the glomerulus[21]. In diffuse proliferative LN, the deposited immune complexes consist of nuclear antigens (e.g., DNA) and high affinity complement fixing IgG antibodies [6,20]. In others, in situ immune complex formation in the subepithelial region is facilitated by binding of cationic nuclear antigens (histones) to anionic basement membrane proteins. Localization of immune complexes in the glomeruli leads to activation of complement cascade and complement mediated injury, activation of procoagulant factors, leukocyte infiltration with release of proteolytic enzymes and production of various cytokines regulating cellular proliferation and matrix synthesis. Glomerular damage may be potentiated by intraglomerular hypertension and activation of coagulation cascade especially in patients with antiphospholipid antibodies (APLA). Recent studies have shown that focal segmental necrotizing glomerular lesions without significant immune complex deposition, resembling a 'pauci immune' pattern with or without ANCAs, can occur in some SLE patients and cause glomerular and vascular damage[23,24].

APLAs directed against phospholipid-β2 glycoprotein complex produce endothelial and platelet dysfunction including reduced production of vasodilatory PGs like prostacycline and other anticoagulant factors, activation of plasminogen, inhibition of protein C or S and enhanced platelet aggregation can also potentiate glomerular and vascular lesions in SLE.

PATHOLOGY OF LUPUS NEPHRITIS:

The histopathology of LN is extremely variable. Pleomorphic appearance of glomeruli in a single biopsy specimen is characteristic of LN[3,9,20]. Glomerular lesion can transform from one pattern to another spontaneously or after treatment. Previously the WHO classification was widely used for almost 30 years. Nowadays the ISN/RPS – 2003 based on LM, IF and electron microscopy findings, is widely used because it addressed many of the limitations of WHO classification[27]. Interobserver reproducibility and the predictive value have been improved with ISN/RPS system[25, 26].

International Society of Nephrology / Renal Pathology classification of lupus nephritis (2003)

CLASS I	**MINIMAL MESANGIAL LUPUS NEPHRITIS** Normal glomeruli by light microscopy, but mesangial immune deposits by immunofluorescence
CLASS II	**MESANGIAL PROLIFERATIVE LUPUS NEPHRITIS** Purely mesangial hypercellularity of any degree or mesangial matrix expansion by light microscopy, with mesangial immune deposits A few isolated subepithelial or subendothelial deposits may be visible by immunofluorescence or electron microscopy, but not by light microscopy
CLASS III	**FOCAL LUPUS NEPHRITIS** Active or inactive focal, segmental or global endo- or extracapillary glomerulonephritis involving <50% of all glomeruli, typically with focal subendothelial immune deposits, with or without mesangial alterations
Class III (A)	Active lesions: focal proliferative lupus nephritis
Class III (A/C)	Active and chronic lesions: focal proliferative and sclerosing lupus nephritis
Class III (C)	Chronic inactive lesions with glomerular scars: focal sclerosing lupus nephritis

CLASS IV	**DIFFUSE LUPUS NEPHRITIS** Active or inactive diffuse, segmental or global endo- or extracapillary glomerulonephritis involving >50% of all glomeruli, typically with diffuse subendothelial immune deposits, with or without mesangial alterations. This class is divided into diffuse segmental (IV-S) lupus nephritis when >50% of the involved glomeruli have segmental lesions, and diffuse global (IV-G) lupus nephritis when >50% of the involved glomeruli have global lesions. Segmental is defined as a glomerular lesion that involves less than half of the glomerular tuft. This class includes cases with diffuse wire loop deposits but with little or no glomerular proliferation.
Class IV-S (A)	Active lesions: diffuse segmental proliferative lupus nephritis
Class IV-G (A)	Active lesions: diffuse global proliferative lupus nephritis
Class IV-S (A/C)	Active and chronic lesions: diffuse segmental proliferative and sclerosing lupus nephritis
Class IV-G (A/C)	Active and chronic lesions: diffuse global proliferative and sclerosing lupus nephritis
Class IV-S (C)	Chronic inactive lesions with scars: diffuse segmental sclerosing lupus nephritis
Class IV-G (C)	Chronic inactive lesions with scars: diffuse global sclerosing lupus nephritis

CLASS V	MEMBRANOUS LUPUS NEPHRITIS
	Global or segmental subepithelial immune deposits or their morphologic sequelae by light microscopy and by immunofluorescence or electron microscopy, with or without mesangial alterations Lupus nephritis may occur in combination with class III or IV in which case both will be diagnosed Class V lupus nephritis may show advanced sclerosis
CLASS VI	**ADVANCED SCLEROTIC LUPUS NEPHRITIS** ≥90% of glomeruli globally sclerosed without residual activity

Class I – Minimal mesangial LN:

It denotes normal appearing glomeruli by LM but with minimal mesangial deposits on IF and EM. Even patients without any evidence of clinical renal disease often have minimal mesangial immune deposits on EM[27].

Class II – Mesangial proliferative LN:

It is characterized by pure mesangial hypercellularity (>3 cells in the mesangium distant from the vascular pole) on LM and mesangial immune deposits on IF and EM[27]. Rarely very minimal subendothelial and subepithelial deposits may be seen on IF or EM.

Class III - Focal lupus nephritis:

It is defined as focal, segmental or global, endocapillary or extracapillary GN affecting less than 50% of the total glomeruli sampled. Focal endocapillary proliferation includes endothelial cells with infiltrating neutrophils and mononuclear cells[27].

This is subclassified into active proliferative (IIIA), inactive sclerosing (IIIC) and active & inactive (IIIA/C) lesions. Active lesions may show cellular crescents, fibrinoid necrosis, nuclear pyknosis or karyorrhexis and rupture of GBM. Hematoxylin bodies, denatured basophilic nuclear materials, are occasionally seen within the necrotizing lesions. Subendothelial immune deposits seen as ‘wire loop’ thickening of capillary walls or large intraluminal masses are known as hyaline thrombi.

Class IV – Diffuse LN:

It is characterized by proliferative changes as described in class III but involving >50% of the glomeruli[27, 28, 29, 30]. This is also subclassified into diffuse segmental, class IV-S in which >50% of the affected glomeruli have segmental lesions and diffuse global, class IV-G in which >50% of the affected glomeruli have global lesions. These IV-S and IV-G lesions are again subclassified into IV-S (A, C, A/C) and IV-G (A, C, A/C) respectively according to the presence of active proliferating and inactive sclerosing lesions.

In general, extensive peripheral capillary wall subendothelial immune deposits and extracapillary proliferation (crescents) are common in class IV LN. GBM double contouring and focal necrotizing and crescentic lesions can occur in class IV as similar to those seen in small vessel vasculitides.

Class V – Membranous LN:

It is characterized by regular subepithelial immune deposits producing membranous pattern[27, 31]. The coexisting changes like mesangial hypercellularity and mesangial immune deposits in most of the cases help to distinguish membranous LN from primary membranous

nephropathy[32]. In early membranous nephropathy only subepithelial immune deposits are detected by IF/EM. Advanced well developed membranous LN lesions have typical diffuse thickening of the capillary walls with spikes. When these lesions are seen along with focal or diffuse endocapillary proliferative lesions and subendothelial immune deposits, they are classified as class V & III and class V & IV, respectively.

Class VI – Advanced sclerosing LN:

It is defined by global glomerular sclerosis affecting >90% of the glomeruli.

Tubulointerstitial disease, vascular lesions like vasculitis and TMA, and lupus podocytopathy are not included in ISN/RPS classification[36, 37, 38, 39].

IMMUNOFLUORESCENCE STUDY:

In LN, immune deposits can be found in the glomeruli, tubules, interstitium and blood vessels. IgG is almost universal along with IgM and IgA in most of the biopsies; C3 and C1q are commonly present. The presence of IgG, IgM and IgA along with C3 and C1q is known as ‘full house’ staining and is highly suggestive of LN. Fibrin is often present in crescents and necrotizing lesions.

ELECTRON MICROSCOPY:

Distribution of immune deposits on EM corresponds to that of IF. Typically these deposits are electron dense and granular. Some have an organized ‘finger print’ like curvilinear microtubular or fibrillar structures composed of bands ranging from 10 to 15 nm in diameter. Tubuloreticular inclusions (IFN α foot prints) are intracellular branching tubular structures measuring 24 nm in diameter seen within the dilated cisternae of the endoplasmic reticulum of glomerular and vascular endothelial cells.

PATHOLOGICAL INDICES OF ACTIVITY AND CHRONICITY:

A semiquantitative histologic scoring system (NIH system) has been developed based on the features of active (potential reversible lesions) and chronic (irreversible lesions) renal damage to predict the outcome of LN.

Pathologic indices of activity and chronicity in lupus nephritis

Chronicity index[a]	**Activity index**[b]
Glomerular sclerosis	Cellular proliferation
Fibrous crescents	Fibrinoid necrosis, karyorrhexis
Tubular atrophy	Cellular crescents
Interstitial fibrosis	Hyaline thrombi, wire loop lesions
	Leukocyte infiltration in glomerulus
	Mononuclear-cell infiltration in interstitium

[a]To obtain a chronicity score, each parameter is graded 0 to 3 depending on severity of involvement, and the grades are added. Glomerular sclerosis and fibrous crescents are graded as follows: 0, absent; 1+, <25% of glomeruli involved; 2+, 25% to 50% of glomeruli involved; 3+, >75% of glomeruli involved. Tubular atrophy and interstitial fibrosis are graded as follows: 0, absent; 1+, mild; 2+, moderate; 3+, severe. The maximum chronicity score is 12.
[b]To obtain an activity score, each parameter is graded 0 to 3 depending on severity of involvement, and the individual grades are added. Fibrinoid necrosis and cellular crescents have been given a weighting factor of 2. The maximum activity score is 24.

Austin and coworkers showed that both high activity index (>12) and high chronicity index (>4) are associated with poor 10 year renal survival rate[33]. A major value of calculating these indices is to compare the features in sequential biopsies and thereby efficacy of therapy and reversibility of the lesion can be assessed[34, 35].

SILENT LN / ANEPHRITIC NEPHRITIS:

It is an extremely uncommon form of LN characterized by active proliferative form of LN on biopsy but no clinical or urinary abnormalities suggestive of active disease and negative lupus serologies[3].

CLINICAL MANIFESTATIONS:

SPECTRUM OF RENAL SYNDROMES:

Renal Manifestations in Patients with Lupus

Manifestation	Prevalance
Proteinuria • Nephrotic syndrome	100% 45–65%
Hematuria • Microhematuria • Red cell casts • Macrohematuria	 80% 10% 1–2%
Cellular casts	30%
Reduced renal function • RPGN • AKI	40–80% 10–20% 1–2%
Hypertension	15–50%
Hyperkalemia	15%
Tubular abnormalities (usually asymptomatic)	60–80%

Patients with class I lupus nephritis often have no evidence of clinical renal disease. Class II patients have mild or minimal clinical renal findings[6, 28]. They may have high anti dsDNA antibody titre or low complement levels, but the urinary sediment is inactive, hypertension is infrequent, proteinuria is usually less than 1g/day and the renal function is usually normal. Nephrotic proteinuria is extremely rare unless there is an evidence of lupus podocytopathy characterized by diffuse foot process effacement on EM [38, 39].

Class III patients often have hypertension, renal failure, proteinuria of >1g/day and active urinary sediments with positive lupus serologies. Nephrotic syndrome is seen in 20 to 30% of the patients at presentation. Patients with less extensive glomerular proliferation, fewer necrotizing features and no crescents are often normotensive and have preserved renal function.

Class IV LN is the most active and severe form of LN and is characterized by high anti dsDNA antibody titre, low complement levels and very active urinary sediments with RBCs and cellular casts[30,40,41]. It carries the worst renal prognosis. Nephrotic syndrome is seen in almost 50% of the patients. Hypertension and renal failure are also more common.

Nephrotic syndrome is the most common presentation of class V LN. Only about 60% of the patients will have elevated anti dsDNA antibody titre and low complement levels[42]. However hypertension and renal impairment may occur without any superimposed proliferative lesions. Renal vein thrombosis and pulmonary embolism can occur in patients with membranous LN[24, 43].

Class VI, end stage LN results from 'burnt out' LN of long duration[6]. Almost all patients have hypertension and renal dysfunction. Anti dsDNA antibody titre and serum complement levels often normalize at this stage.

SEROLOGICAL TESTS IN LUPUS:

ANA and anti dsDNA antibodies are included in the ARA criteria for diagnosing SLE and are commonly used to monitor the disease activity[44]. ANA is the most sensitive (>90%) screening test for SLE but not specific and it can be present in other rheumatological and non rheumatological disorders[3, 4,5,20]. Neither the particular pattern of ANA on IF (homogenous, speckled, nucleolar or rim) nor the titre of ANA correlates well with the presence of severity of LN.

Anti dsDNA antibodies are more specific but less sensitive and are found in almost three fourths of the untreated SLE patients[44]. These may

be detected by Farr radioimmunoassay, IF test directed against the DNA in the kinetoplast of Crithidia luciliae or by ELISA[19, 44]. High anti dsDNA antibody titre correlates well with clinical activity and flare of LN[14, 44].

Anti Sm antibodies are very specific for SLE but are found only in 25% of patients. AntiC1q antibodies also have been associated with activity of LN[19, 44]. Anti Ro/SSA and anti La/SSB antibodies are present in 25 to 30% and 5 to 15% of SLE patients, respectively. Maternal Anti Ro/SSA antibodies are important in the setting of neonatal lupus which is usually associated with cardiac conduction abnormalities in newborns[45.] Anti histone antibodies are present in >90% of patients with drug induced lupus[46].

Serum levels of total hemolytic component (CH50) and complement components C3 and C4 are often decreased in patients with active SLE and active LN[9, 44]. Both C3 and C4 are depressed or the C4 alone is preferentially depressed in LN. Serial monitoring of complement levels, if declining, helps in predicting a flare in LN and normalization of depressed levels is often associated with improved renal outcome[48]. Low C4 and normal C3 reflect hereditary C4 deficiency[49]. One third to one half of the patients will have antiphospholipid antibodies (APLAs) [50, 51, 52]. These are lupus anticoagulant and anticardiolipin antibodies. Lupus anticoagulant is best assessed by dilute Russell's viper venom test

(DRVT). In SLE patients with pregnancy, presence of APLAs is associated with high fetal loss[53].

COURSE AND PROGNOSIS OF LN:

The course of LN is extremely varied with from <5% to >60% developing renal failure [29, 42,47,54,55]. The natural course of LN is determined by the initial pattern and severity of renal involvement as modified by therapy, flares of disease activity and complications of treatment. In general, class I and II have excellent prognosis[3, 47]. Class III patients have extremely varied course. Those with mild proliferation respond well to therapy and only <5% progress to renal failure over 5 years[3, 4, 6,42,47,56].

Patients with more proliferation, necrotizing features or crescent formation have a prognosis similar to class IV LN. Those with diffuse proliferative LN have the least favorable prognosis in older series[20, 29, 30, 42]. But nowadays the prognosis has markedly improved with modern immunosuppressive agents, with renal survival rate exceeding >90% at 5 years in some series[3, 30, 56, 57]. The factors associated with progressive renal failure are old age, male sex, black race, anemia with hematocrit <26%, serum creatinine >2.4 mg/dl, high activity (>7) and chronicity (>3) on histopathology and the severity of tubulointerstitial damage[40, 58, 59].

Class V LN – Natural history is not clear and early studies showed better prognosis in membranous LN when compared to active proliferative lesions[28]. One U.S study found that 10 year survival rate was 72% for pure membranous LN and only 20 to 48% for those having superimposed proliferative lesions (class III + V or class IV + V)[31]. But only Italian studies found the 10 year survival to be 93% for pure membranous LN[60].

TREATMENT OF LUPUS NEPHRITIS:

Patients with ISN/RPS classes I and II have an excellent prognosis and no specific therapy directed to the kidney. An exception to this is lupus podocytopathy which requires a short course of high dose corticosteroid therapy as in MCD [39]. Class III patients with mild proliferation respond well to a short course of high dose corticosteroids or a brief course of other immunosuppressive agents. Those with necrotizing features and crescents require aggressive therapy as in class IV LN.

Patients with class IV LN require combination therapy of corticosteroids and immunosuppressive agents[6, 30, 41, 47,56,61,62]. Treatment is divided into induction and maintenance phases. Corticosteroids and intravenous cyclophosphamide[65,66,67,68,69] or MMF[37,38,39,40,41,42] are used in the induction phase to induce remission and azathioprine or MMF is used along with low dose prednisolone in the maintenance phase to avoid

relapse and disease flares in the future[63,64]. For the patients with combined class IV & V lesions, multitargeted regimen of tacrolimus, MMF and corticosteroids can be used[76].

BIOLOGICAL AGENTS IN LUPUS NEPHRITIS[4, 77, 80, 81,164,167,168:]

1. Rituximab (chimeric anti CD20 monoclonal antibody)
2. Abatacept (CTLA4 Ag)
3. Belimumab (B cell stimulating cytokine inhibitor)
4. Ocrelizumab (a fully humanized anti CD20 monoclonal antibody)
5. Epratuzumab (a humanized anti CD22 monoclonal antibody)
6. Eculizumab (anti C5a antibody)
7. Abetimus (prevents the anti dsDNA antibody formation)

OTHER THERAPIES:

IV Ig and plasmapheresis may be useful in some patients. Total lymphoid irradiation, immunoablation by high dose cyclophosphamide and antilymphocyte globulin with or without reconstitution with autologous stem cells may be tried in resistant lupus[78, 79].

MANAGEMENT OF MEMBRANOUS LN:

A short course of cyclosporine and low dose steroids along with ACE inhibitors or ARBs and statins can be used in patients with subnephrotic proteinuria and preserved renal function. For patients with nephrotic proteinuria and at higher risk for progressive renal disease, options include cyclosporine, MMF, azathioprine or i.v cyclophosphamide along with corticosteroids[82].

AIMS & OBJECTIVES

1. To evaluate the correlation between serological profile and histopathology of lupus nephritis.
2. To find out the class of LN which has significant correlation with serological profile.
3. To define the positive predictive value of anti dsDNA and low complement levels with proliferative lupus nephritis.
4. To assess whether renal biopsy will alter the treatment plan in proliferative lupus nephritis.

MATERIALS AND METHODS

Study design: A prospective study

Period of study: one year – Jan 2012 to Dec 2012

Study setting: Nephrology Dept, Kilpauk medical college, Chennai.

Ethical committee approval: obtained from ethical committee chairman, Kilpauk medical college.

Consent: obtained informed consent including for renal biopsy.

Subjects: All ANA positive female patients with evidence of renal involvement admitted in our dept. of Nephrology.

Study criteria:

Inclusion criteria:

All ANA positive female SLE patients fulfilling ARA criteria between 15 and 45 years of age group with any one of the following abnormalities-

1. Proteinuria (spot urine PCR >0.5)

2. Microscopic hematuria (≥ 3 RBCs/hpf)

3. Increased serum creatinine (>1.2 but ≤ 1.8 mg/dl)

Exclusion criteria:

1. Male SLE patients

2. Patients below 15 and above 45 years of age group

3. ANA negative lupus patients

4. Serum creatinine >1.8 mg/dl

Collaborating departments:

1. Dept of Rheumatology
2. Dept of Medicine
3. Dept of Pathology
4. Dept of Microbiology
5. Dept of Biochemistry

Study protocol:

All the patients who fulfilled the study criteria were included in the study after getting informed consent for renal biopsy. A well designed proforma was used to collect the demographic and clinical details of the patients.

Investigations and methodologies:

Apart from basic workup like urine analysis,CBC,RFT,LFT,ECG,X ray chest and USG KUB, the following other investigations have been done in all patients.

1. Viral markers – HIV ELISA, HBsAg, antiHCV.
2. Serological tests for SLE –
    - Anti dsDNA antibody – done by Immunofluorescence method using the DNA of the kinetoplast of Crithidia luciliae.
    - Serum complement levels for C3, C4 – by nephalometric method.
    - ANA has been done already before enrolling the patient into the study – by indirect immunofluorescence method using Hep 2 cells.
    - Percutaneous renal biopsy – specimen analysed by LM and IF.
    - Proteinuria was assessed by dipstick method.
    - Serum creatinine was measured by modified Jaffe's kinetic method.

Statistical analysis:

Data analysis was done by using SPSS 17 software. Univariate analysis was done by chi square test. Multivariate analysis was done by logistic regression method.

RESULTS AND ANALYSIS

In our study, 50 female SLE patients were included.

1. **Age distribution:**

Of 50 patients,25 (50%)were in the age group of 15 to 25 years, 17 in 26 to 35 years and 8 were in 36 to 45 years.

Age distribution

Age	Frequency	Percent
15-25	25	50.0
26-35	17	34.0
36-45	8	16.0
Total	50	100.0

2. **Proteinuria:**

All the 50 patients (100%) had proteinuria in our study.

3. **CLASS OF LN IN Renal biopsy:**

35 patients (70%) had class IV lupus nephritis, 7 (14%) class II, 4(8%) class V and 4 patients (8%) had class IV & V on renal biopsy. No one had class III LN in our study. Totally 39 patients (78%) had proliferative LN (class IV and class IV & V).

Class of LN in Renal Biopsy

Class	Frequency	Percent
II	7	14.0
IV	35	70.0
V	4	8.0
IV and V	4	8.0
Total	50	100.0

Proliferative LN - Classes IV, IV & V

	Frequency	Percent
Absent	11	22.0
Present	39	78.0
Total	50	100.0

4. Microscopic hematuria and its correlation with the histopathology of LN:

Only 37 patients (74%) of LN had microscopic hematuria. 29 of 35 patients (82.9%) with class IV, 3 of 4 patients (75%) with class IV&V, 2 of 7 patients (28.6%) with class II and 3 of 4 patients (75%) with class V LN had microscopic hematuria. 32 of 39 patients (82%) with proliferative LN had microscopic hematuria (P Value- 0.03).

Microscopic hematuria

	Frequency	Percent
Present	37	74.0
Absent	13	26.0
Total	50	100.0

Class of LN & Microscopic hematuria - Correlation

Renal Biopsy	Microscopic hematuria		Total	P Value
	Present	Absent		
II	2	5	7	
	28.6%	71.4.0%	100.0%	
IV	29	6	35	
	82.9%	17.1%	100.0%	0.03
V	3	1	4	
	75.0%	25.0%	100.0%	
IV and V	3	1	4	
	75.0%	25.0%	100.0%	
Total	37	13	50	
	74.0%	26.0%	100.0%	

5. **Serum creatinine and its correlation with the histopathology of LN:**

Only 17 of 50(34%) patients had increased serum creatinine. 16 of 35(45.7%) patients with class IV, 1of 4(25%) patients with class V had ↑ed serum creatinine. None of the patients with class II and class IV& V had ↑ed serum creatinine (P Value- 0.047).

Serum creatinine

	Frequency	Percent
Normal	33	66.0
Increased	17	34.0
Total	50	100.0

Class of LN & Serum creatinine - Correlation

Renal Biopsy		Serum creatinine		Total	p value
		Normal	Increased		
II	Count	7	0	7	0.047
	% within Renal Biopsy	100.0%	0%	100.0%	
IV	Count	19	16	35	
	% within Renal Biopsy	54.3%	45.7%	100.0%	
V	Count	3	1	4	
	% within Renal Biopsy	75.0%	25.0%	100.0%	
IV and V	Count	4	0	4	
	% within Renal Biopsy	100.0%	0%	100.0%	
Total	Count	33	17	50	
	% within Renal Biopsy	66.0%	34.0%	100.0%	

6. **Anti dsDNA and its correlation with the histopathology of LN:**

Of 50 patients with LN, 41(82%) had anti dsDNA positivity. 34 of 35 patients (97.1%) with class IV, all the 4 patients (100%) with class IV&V, 1 of 7 patients (14.3%) with class II and 2of 4 patients (50%) with class V LN had anti dsDNA positivity. Totally 38 of 39 patients (97.4%) with proliferative LN had anti dsDNA positivity (P Value < 0.001).

Anti dsDNA

	Frequency	Percent
Negative	9	18.0
Positive	41	82.0
Total	50	100.0

Class of LN & Anti dsDNA - Correlation

Renal Biopsy		Anti dsDNA		Total	P Value
		Negative	Positive		
II	Count	6	1	7	<0.001
	% within Renal Biopsy	85.7%	14.3%	100.0%	
IV	Count	1	34	35	
	% within Renal Biopsy	2.9%	97.1%	100.0%	
V	Count	2	2	4	
	% within Renal Biopsy	50.0%	50.0%	100.0%	
IV and V	Count	0	4	4	
	% within Renal Biopsy	0%	100.0%	100.0%	
Total	Count	9	41	50	
	% within Renal Biopsy	18.0%	82.0%	100.0%	

Proliferative LN Classes IV, IV& V and Anti dsDNA- correlation

Renal Biopsy – IV, IV & V		Anti dsDNA		Total	P Value
		Negative	Positive		
Absent	Count	8	3	11	<0.001
	% within Renal Biopsy - IV	72.7%	27.3%	100.0%	
Present	Count	1	38	39	
	% within Renal Biopsy - IV	2.6%	97.4%	100.0%	
Total	Count	9	41	50	
	% within Renal Biopsy - IV	18.0%	82.0%	100.0%	

7. Serum C3 and its correlation with the histopathology of LN:

Of 50 patients with LN, 34(68%) had low C3 level in serum. 29 of 35 patients (82.9%) with class IV, all the 4 patients (100%) with class IV&V and 1 of 4 patients (25%) with class V LN had low C3 level in serum. But none of the patients with class II LN had low C3 level. Totally 33 of 39 patients (84.6%) with proliferative LN had low C3 level (P Value < 0.001).

Serum C3

	Frequency	Percent
Normal	16	32.0
Decreased	34	68.0
Total	50	100.0

Class of LN & serum C3 - correlation

Renal Biopsy		C3			P Value
		Normal	Decreased	Total	
II	Count	7	0	7	<0.001
	% within Renal Biopsy	100.0%	0%	100.0%	
IV	Count	6	29	35	
	% within Renal Biopsy	17.1%	82.9%	100.0%	
V	Count	3	1	4	
	% within Renal Biopsy	75.0%	25.0%	100.0%	
IV and V	Count	0	4	4	
	% within Renal Biopsy	0%	100.0%	100.0%	
Total	Count	16	34	50	
	% within Renal Biopsy	32.0%	68.0%	100.0%	

Proliferative LN Classes IV, IV& V and serum C3- correlation

Renal Biopsy – IV, IV& V		C3			P Value
		Normal	Decreased	Total	
Absent	Count	10	1	11	<0.001
	% within Renal Biopsy - IV	90.9%	9.1%	100.0%	
Present	Count	6	33	39	
	% within Renal Biopsy – IV	15.4%	84.6%	100.0%	
Total	Count	16	34	50	
	% within Renal Biopsy - IV	32.0%	68.0%	100.0%	

8. Serum C4 and its correlation with the histopathology of LN:

Of 50 patients with LN, 37(74%) had low C4 level in serum. 30 of 35 patients (85.7%) with class IV, all the 4 patients (100%) with class IV&V and 3 of 4 patients (75%) with class V LN had low C4 level in serum. But none of the patients with class II LN had low C4 level. Totally 34 of 39 patients (87.2%) with proliferative LN had low C4 level (P Value < 0.001).

Serum C4

	Frequency	Percent
Normal	13	26.0
Decreased	37	74.0
Total	50	100.0

Class of LN & serum C4 - correlation

Renal Biopsy		C4		Total	P Value
		Normal	Decreased		
II	Count	7	0	7	<0.001
	% within Renal Biopsy	100.0%	0%	100.0%	
IV	Count	5	30	35	
	% within Renal Biopsy	14.3%	85.7%	100.0%	
V	Count	1	3	4	
	% within Renal Biopsy	25.0%	75.0%	100.0%	
IV and V	Count	0	4	4	
	% within Renal Biopsy	0%	100.0%	100.0%	
Total	Count	13	37	50	
	% within Renal Biopsy	26.0%	74.0%	100.0%	

Proliferative LN Classes IV, IV& V and serum C4 - correlation

Renal Biopsy – IV, IV&V		C4		Total	P value
		Normal	Decreased		
Absent	Count	8	3	11	<0.001
	% within Renal Biopsy - IV	72.7%	27.3%	100.0%	
Present	Count	5	34	39	
	% within Renal Biopsy - IV	12.8%	87.2%	100.0%	
Total	Count	13	37	50	
	% within Renal Biopsy - IV	26.0%	74.0%	100.0%	

9. Logistic regression analysis:

It was used to analyze the correlation between all the three variables in serology (anti dsDNA positivity, low C3 and low C4) and proliferative form (class IV and class IV&V) of LN. Positive predictive value of these variables was 97.4%. All the three variables, positive anti dsDNA, low C3 and low C4 independently predicted proliferative LN with significant P values, 0.029,0.030 and 0.049, respectively.

Categorical Variables Coding

Variables	Comment	Frequency
C4	Normal	13
	Decreased	37
C3	Normal	16
	Decreased	34
Anti dsDNA	Negative	9
	Positive	41

Classification Table

Observed		Predicted		
		Renal Biopsy – IV		Percentage Correct
		Absent	Present	
Renal Biopsy - IV	Absent	9	2	81.8
	Present	1	38	97.4
Overall Percentage				94.0

Variables in the Equation

	B	S.E.	Wald	df	Sig.	Exp(B)
ANTI dsDNA(1)	-3.985	1.829	4.744	1	.029	.019
C3(1)	-3.126	1.444	4.688	1	.030	.044
C4(1)	-2.952	1.518	3.783	1	.049	.052
Constant	5.028	1.522	10.921	1	.001	152.661

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Of 39 patients with proliferative LN, 28(72%) had the combination of positive anti dsDNA, low C3 and low C4 levels in serum. But none of the patients with class II and class V LN had similar combination of serology.

DISCUSSION

Most of the patients with active proliferative lupus nephritis have high titres of anti dsDNA and low serum complement levels [30, 40, 41].

We have studied 50 ANA positive female SLE patients with any one of the evidences of LN (proteinuria, microscopic hematuria or increased serum creatinine) to evaluate the correlation between serological profile and histopathology of LN.

Majority (25 patients, 50%) were in the age group between 15 and 25 years. All patients had significant proteinuria (>500 mg/day).

Masakki nakano et al, reported that 83.8% (31 of 37 pts) of patients had class IV LN on biopsy[87]. In our study, 70% (35 pts) had class IV and 8% (4 pts) had combined class IV&V. Totally 78% (39 of 50 pts) had proliferative LN.

Elene Gonzalo, et al reported that 86.2% (50 of 58 pts) with proliferative LN had microscopic hematuria[89]. In our study, 82% (32 of 39 pts) of patients with proliferative LN had microscopic hematuria.

Salwa Ibrahim and Ahmed Fayed reported renal impairment in 85% of the patients with LN[88]. In our study, it was 34% (17 of 50 pts). Masakki nakano et al, found that 67% (25 of 37 pts) of patients with proliferative

LN had renal insufficiency[87]. In our study, 41% (16 of 39 pts) of patients with proliferative LN had increased serum creatinine.

Vandana et al, reported high prevalence of antinucleosomal (88%) and anti dsDNA (80%) antibodies in SLE patients with active proliferative LN. But it was not statistically significant between LN group and non LN group ($p > 0.05$)[83]. Cornelia Bigler et al, also reported high prevalence of anti dsDNA antibodies (94.3%) in SLE patients with active proliferative LN and it was statistically significant when compared to non LN group ($p < 0.001$)[84]. Gonzalo et al reported that 84.5% (49 of 58 pts) with proliferative LN had anti dsDNA positivity [89]. In our study, the prevalence of anti dsDNA was 97.1% in LN and 97.4% (38 of 39 pts) in proliferative LN ($p < 0.001$).

In a study conducted by Carlos Franco et al, the prevalence of hypocomplementemia was 91.4% with class IV LN ($p = 0.05$)[85]. Gonzalo et al also reported high prevalence (91.2%) of hypocomplementemia with proliferative LN[89]. In our study, C3 level was low in 68% of patients with LN and 84.6% with proliferative LN ($p < 0.001$). C4 level was low in 74% of patients with LN and 87.2% with proliferative LN ($p < 0.001$).

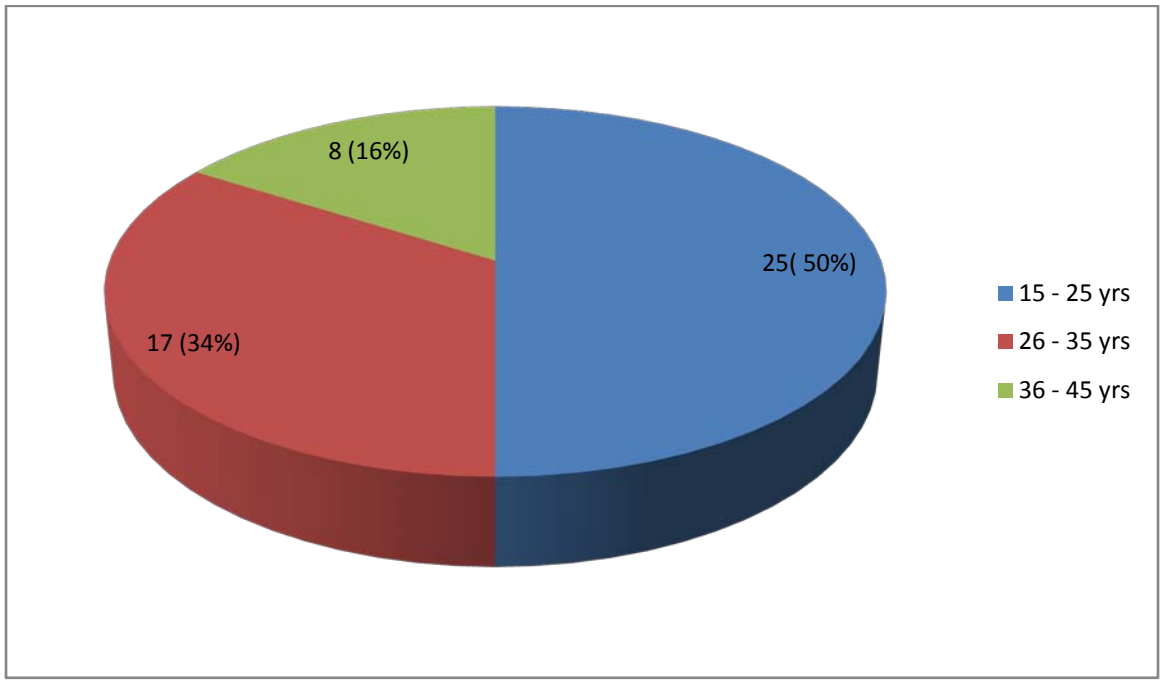
Austin and Illei quoted that anti dsDNA was commonly absent with variable hypocomplementemia in membranous LN and anti dsDNA positivity with hypocomplementemia in proliferative LN[86].

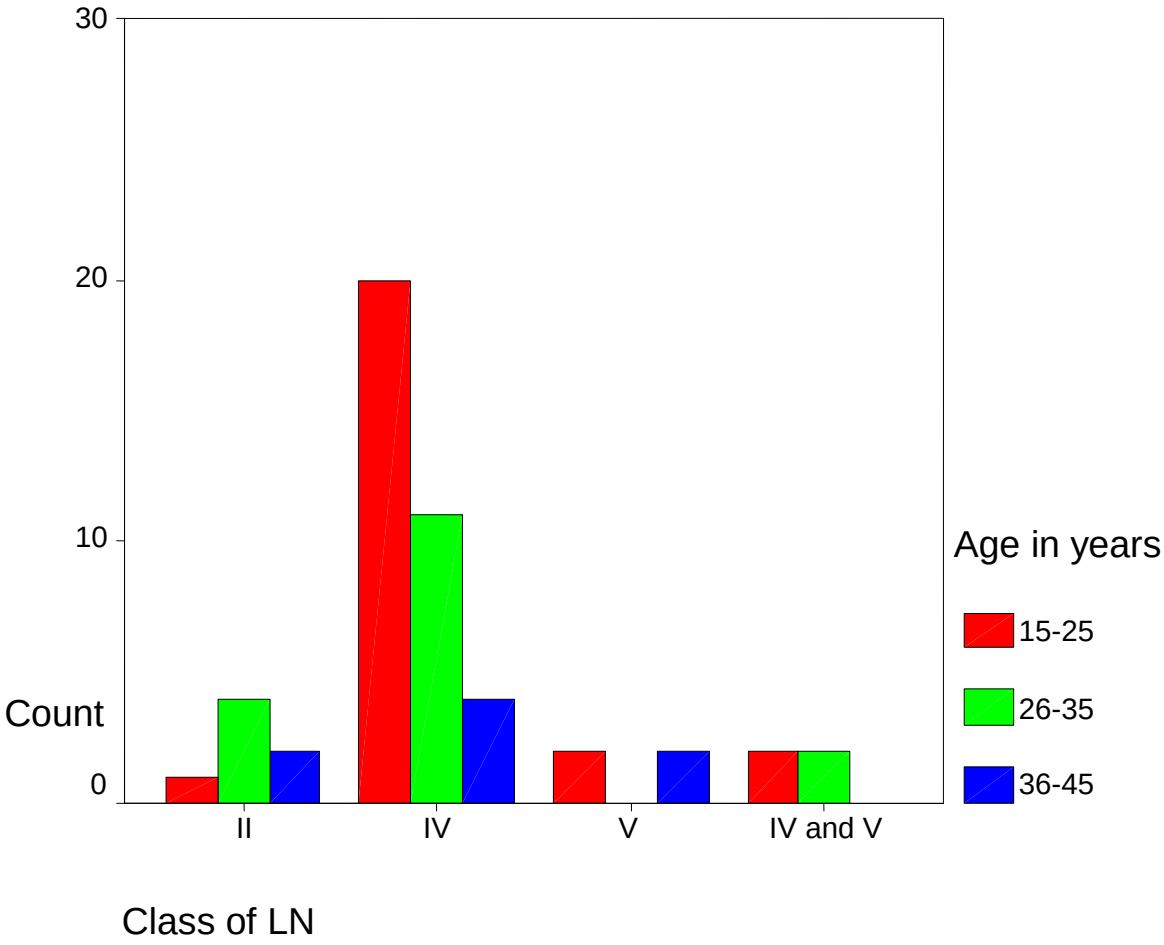
In our study, 72%(28 of 39 pts) of the patients with active proliferative LN(class IV, IV&V) had the combination of anti dsDNA positivity, low C3 and low C4 levels but none of the patients with class II or class V LN had this combination of serology. All these three serological markers had significant correlation with proliferative LN (class IV, IV&V) and the positive predictive value was 97.4% ($p<0.05$).

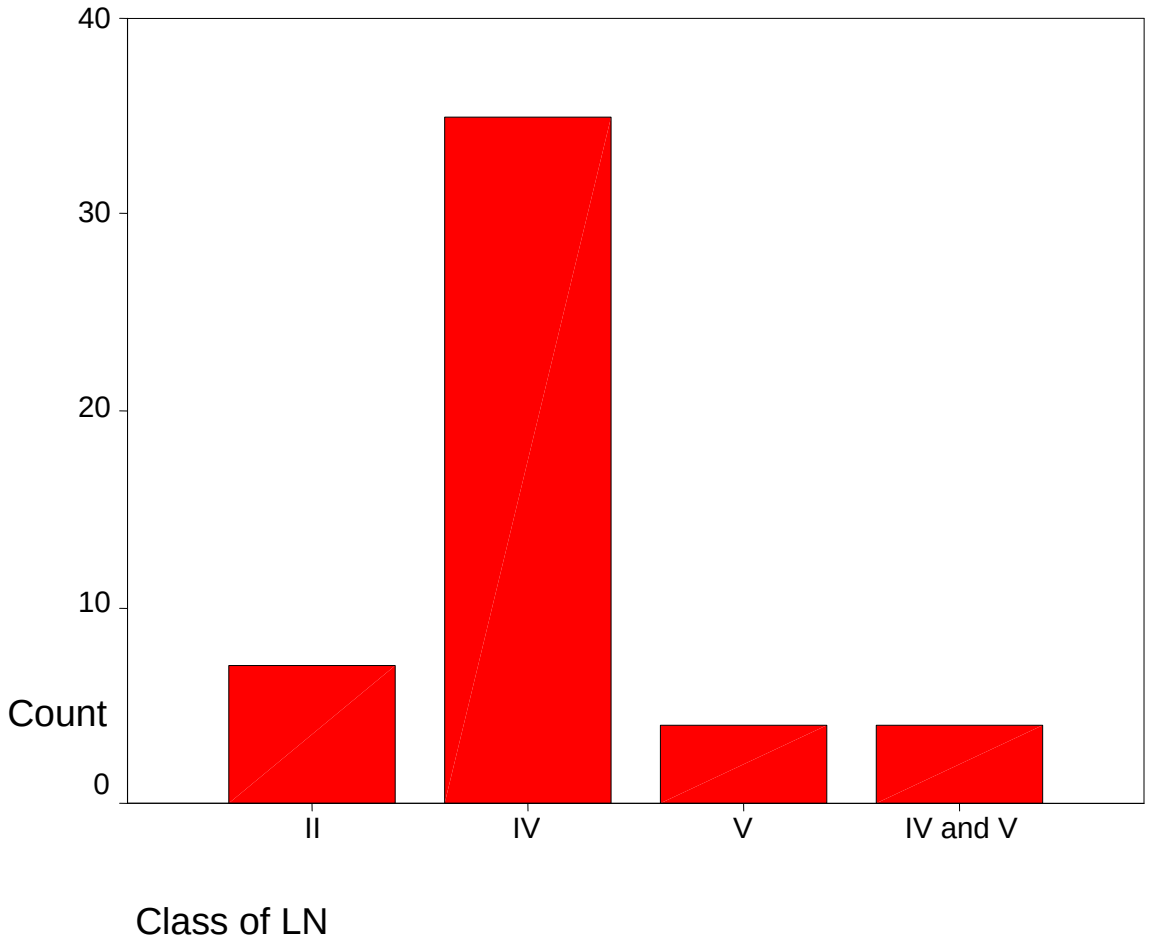
CONCLUSION

- In our study, serological profile of SLE had significant correlation with histopathology of lupus nephritis.
- Anti dsDNA, low C3 and low C4 had significant independent correlation ($p<0.05$) with proliferative LN (class IV, IV&V).
- Positive predictive value of all these three serological markers put together for proliferative LN was 97.4%.
- None of the patients with class II or class V LN had the combination of anti dsDNA positivity, low C3 and low C4 levels.
- So, we may suggest that serology alone is sufficient to predict the proliferative LN and there can be a case for starting immunosuppressive therapy without biopsy in a known SLE patient with evidence of LN and positive serology.

AGE DISTRIBUTION




30
20
10
0
Count
II
IV
V
IV and V
Class of LN
Age in years
15-25
26-35
36-45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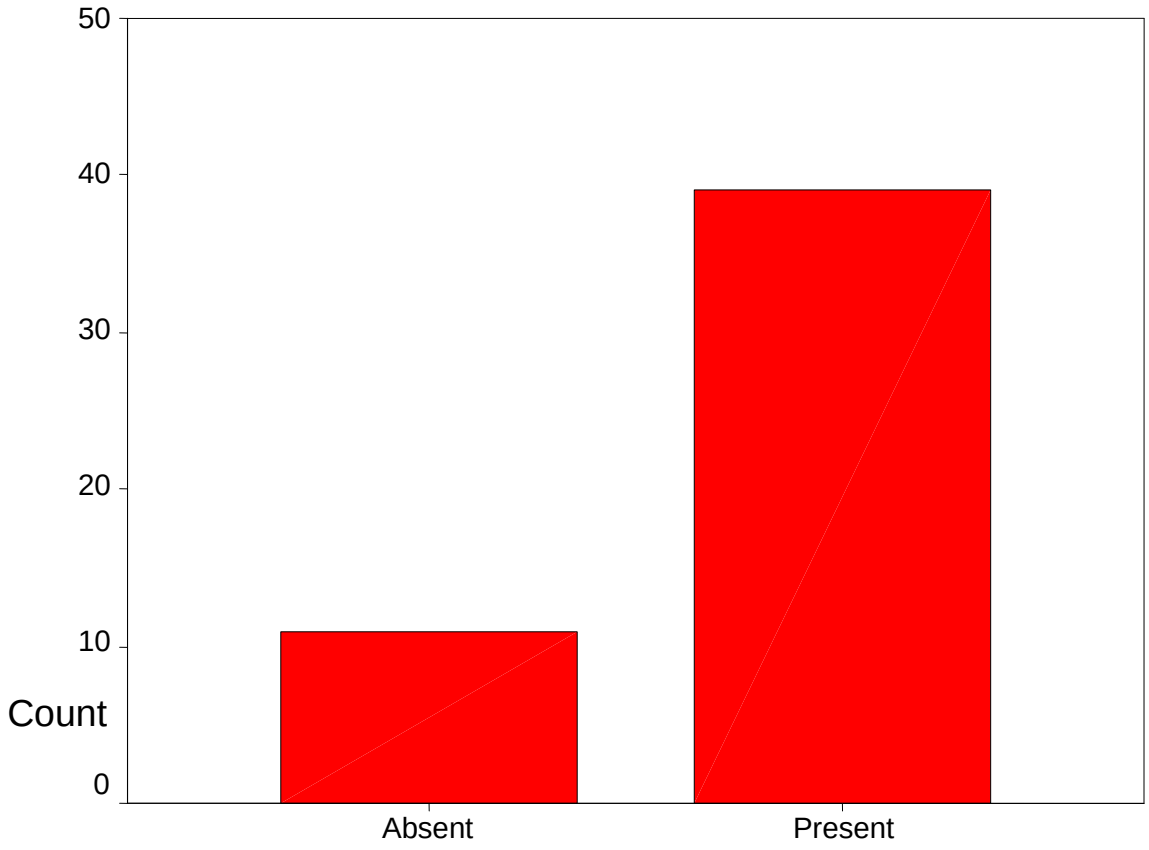
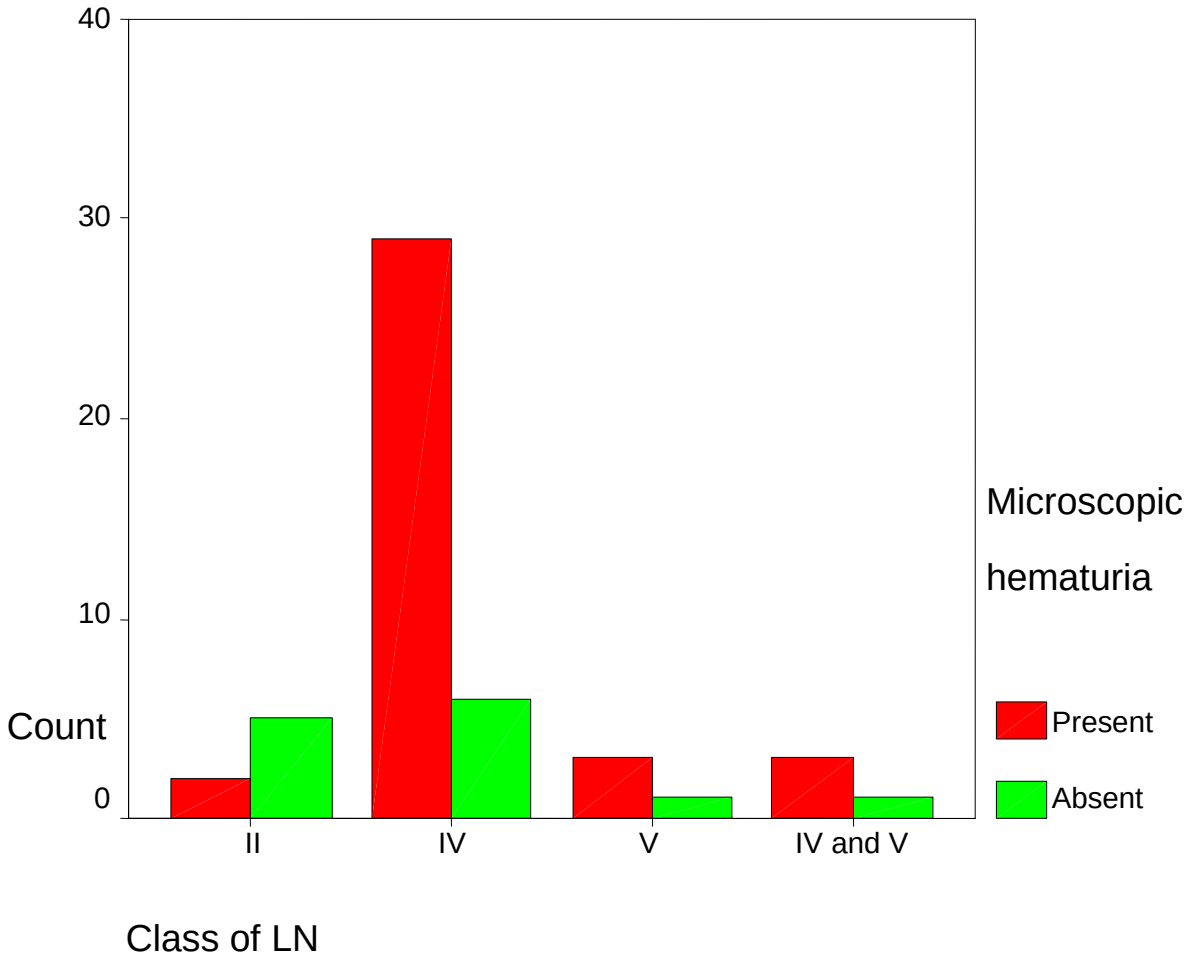
30
20
10
0
Count
II
IV
V
IV and V
Class of LN



Proliferative LN – Classes IV, IV&V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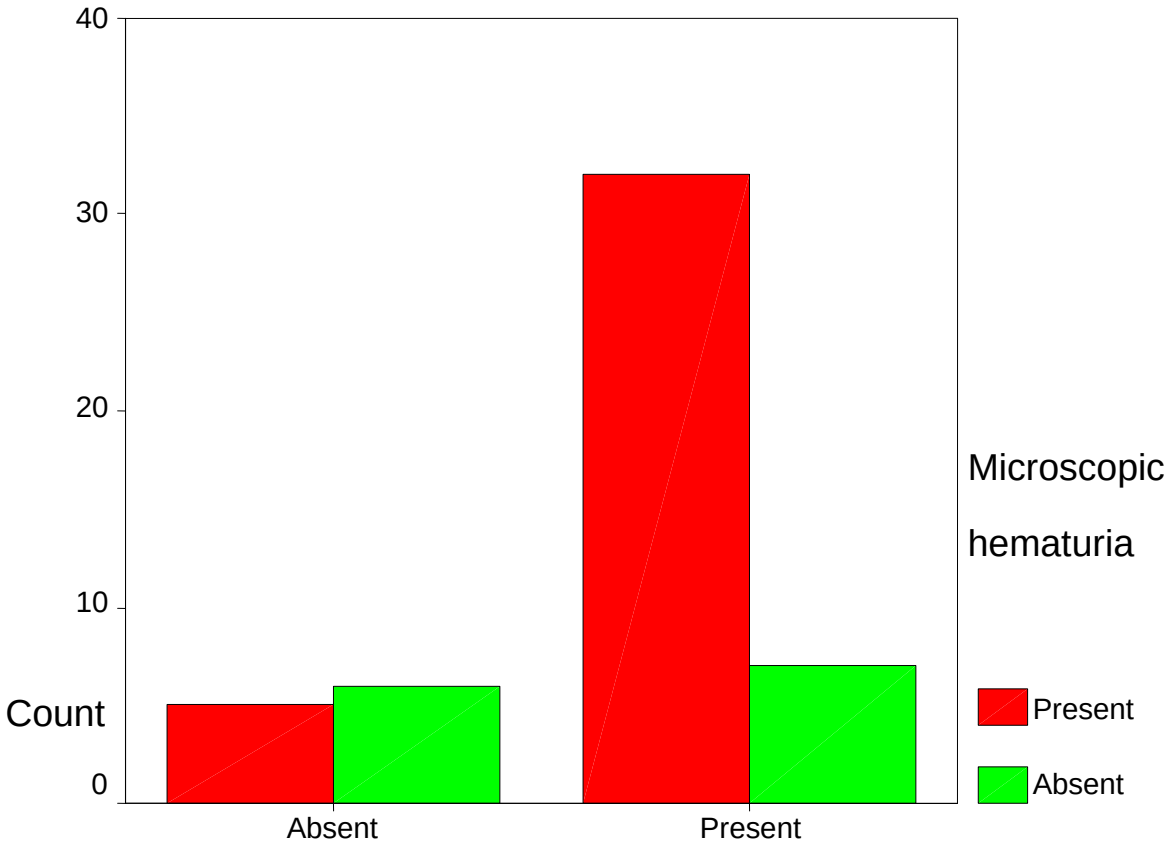
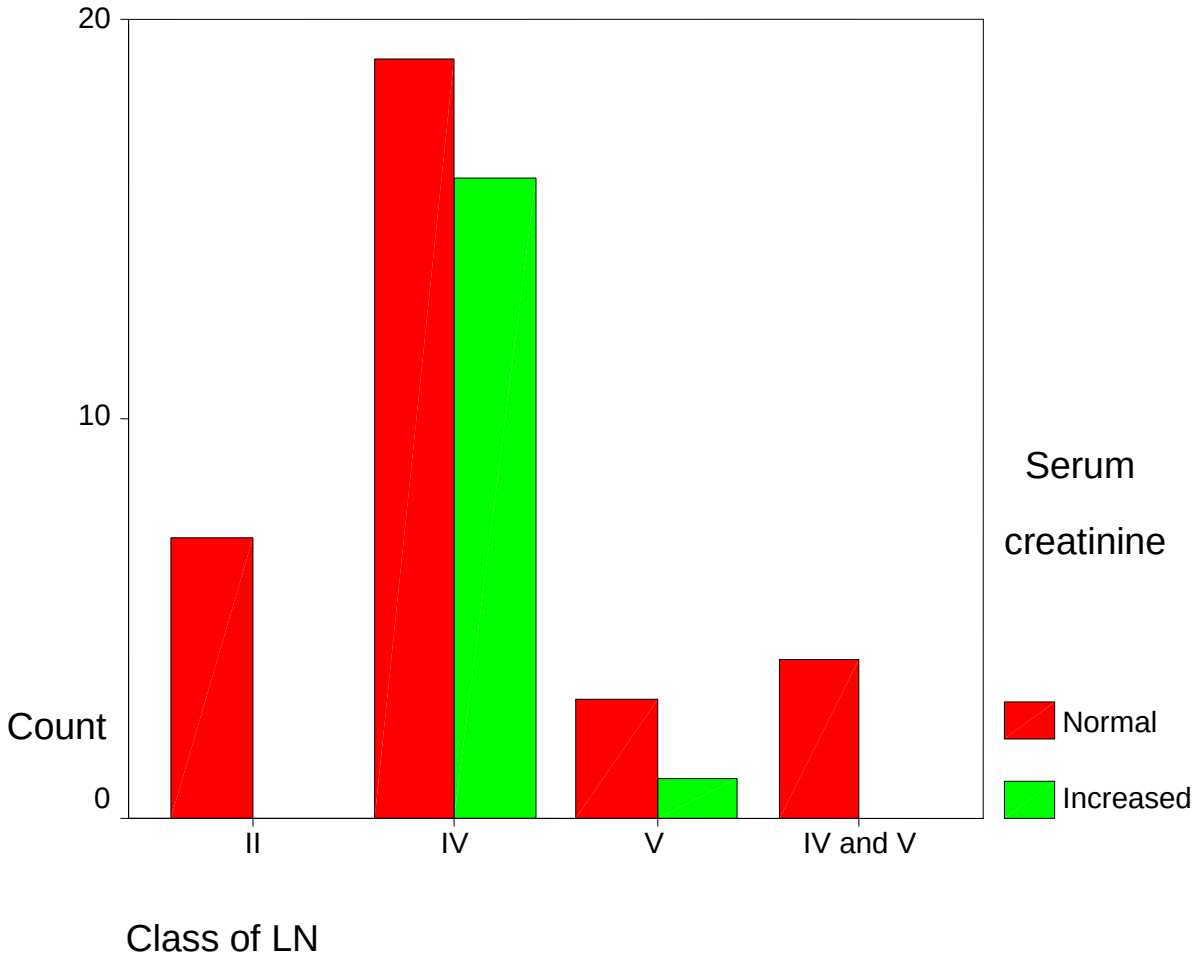
30
20
10
0
Count
II
IV
V
IV and V
Class of LN
Microscopic
hematuria
Present
Absent



Proliferative LN – Classes IV, IV&V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Count
II
IV
V
IV and V
Class of LN
Serum creatinine
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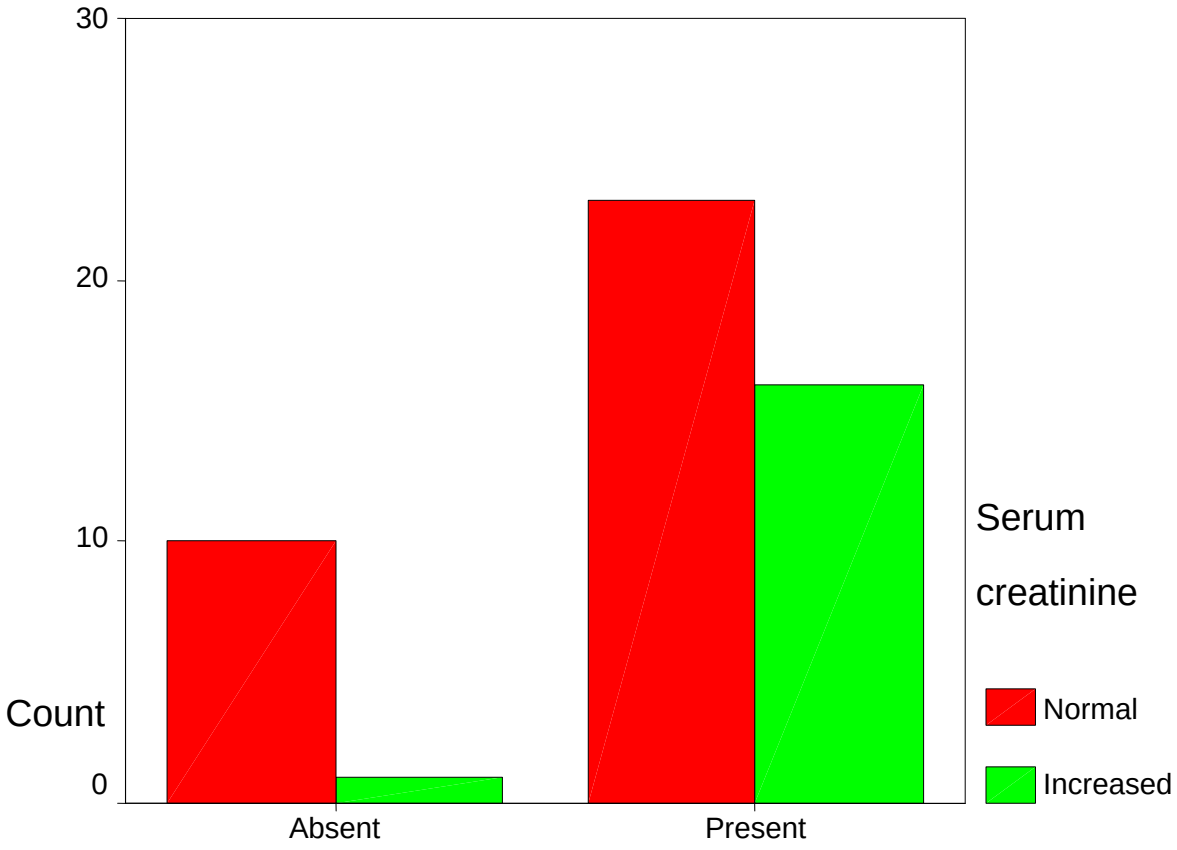
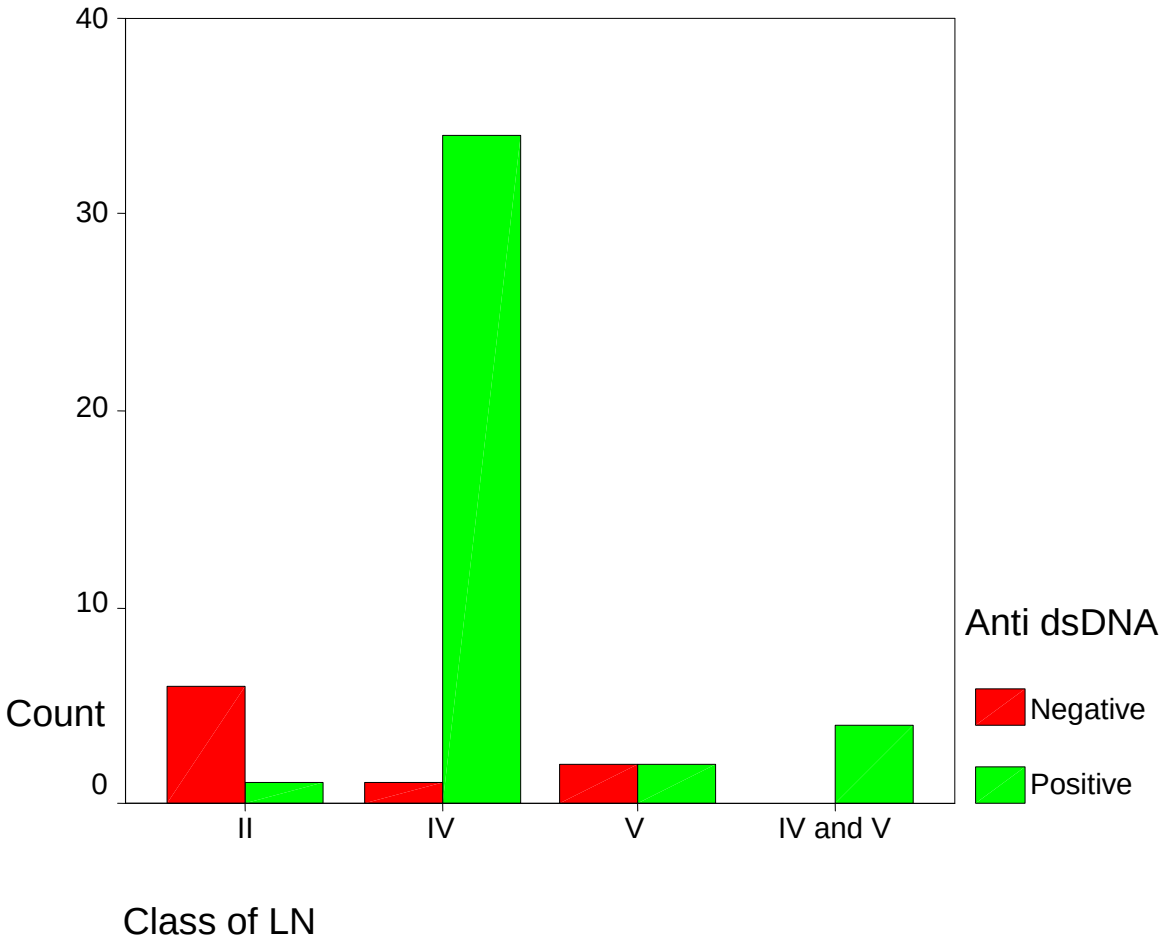
Increased



Proliferative LN – Classes IV, IV&V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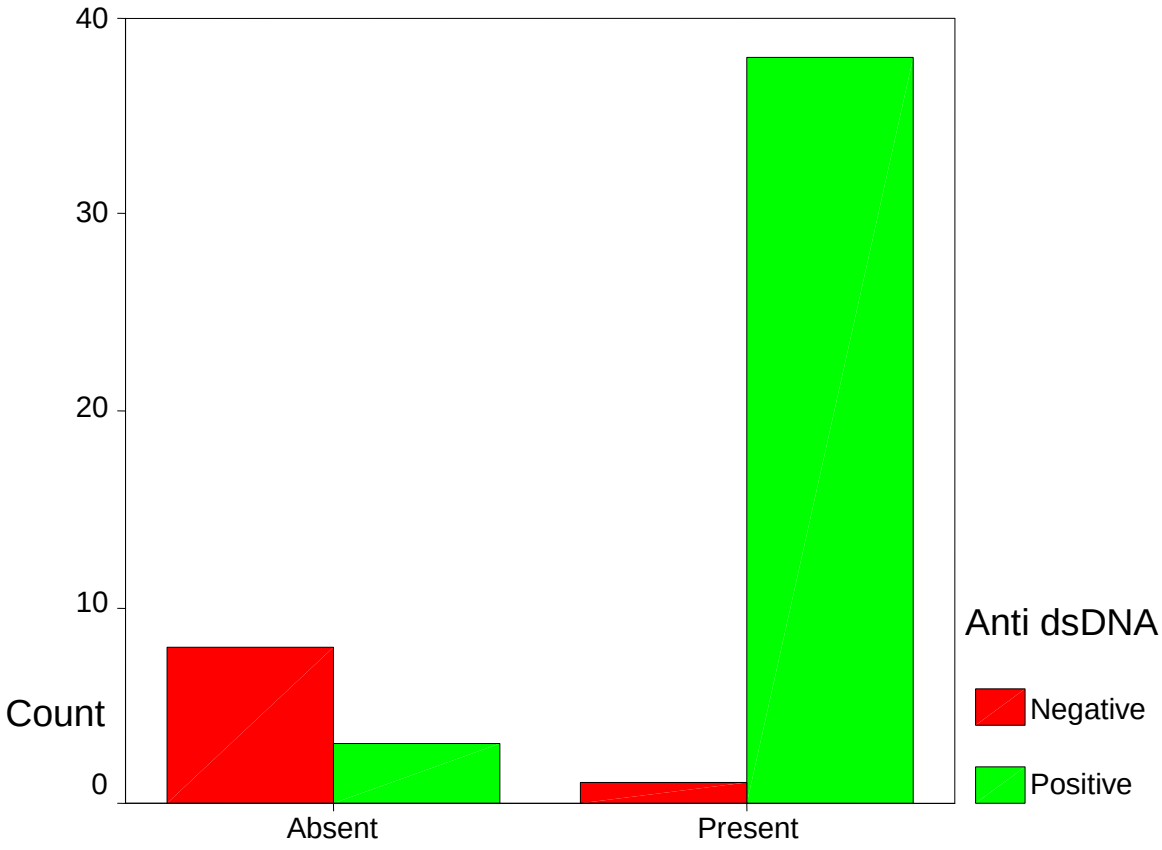
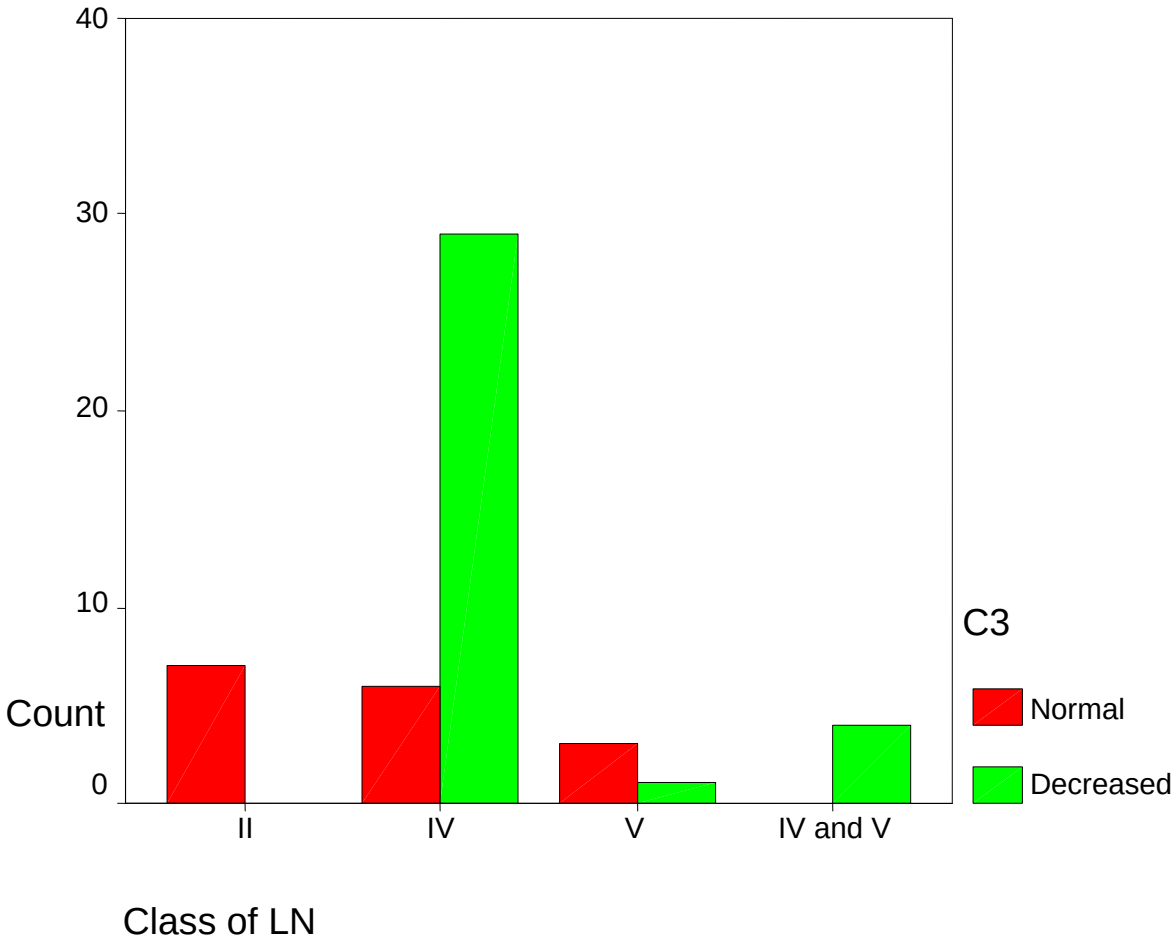
IV
V
IV and V
Class of LN
Anti dsDNA
Negative
Positive



Proliferative LN – Classes IV, IV&V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30
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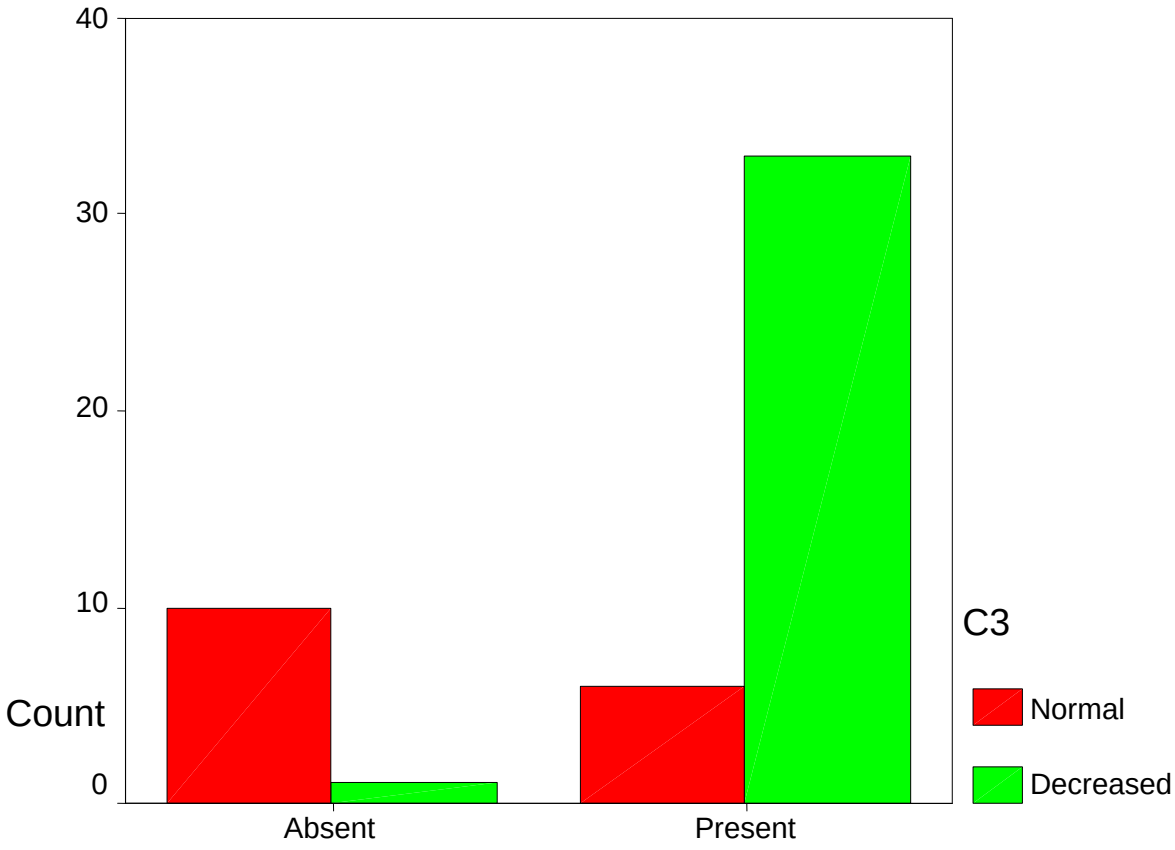
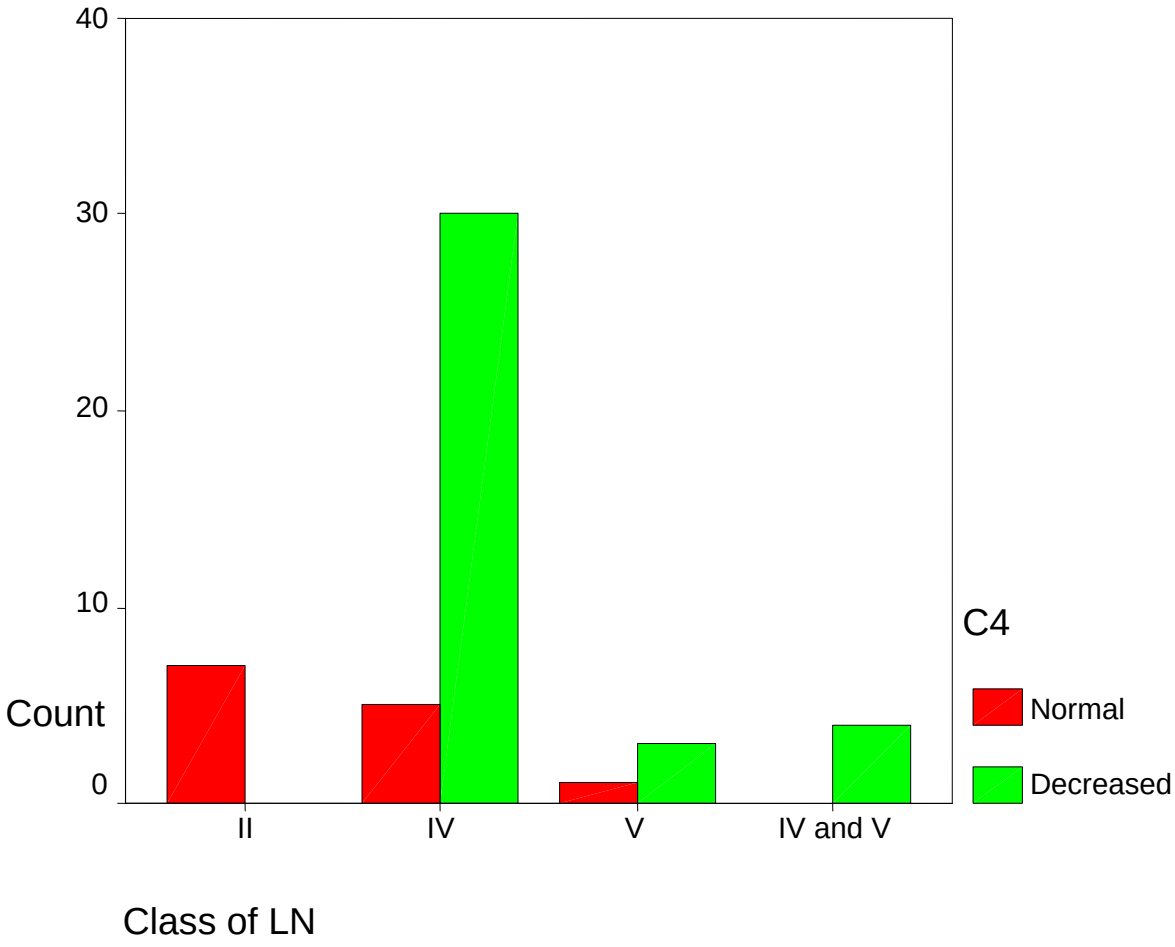
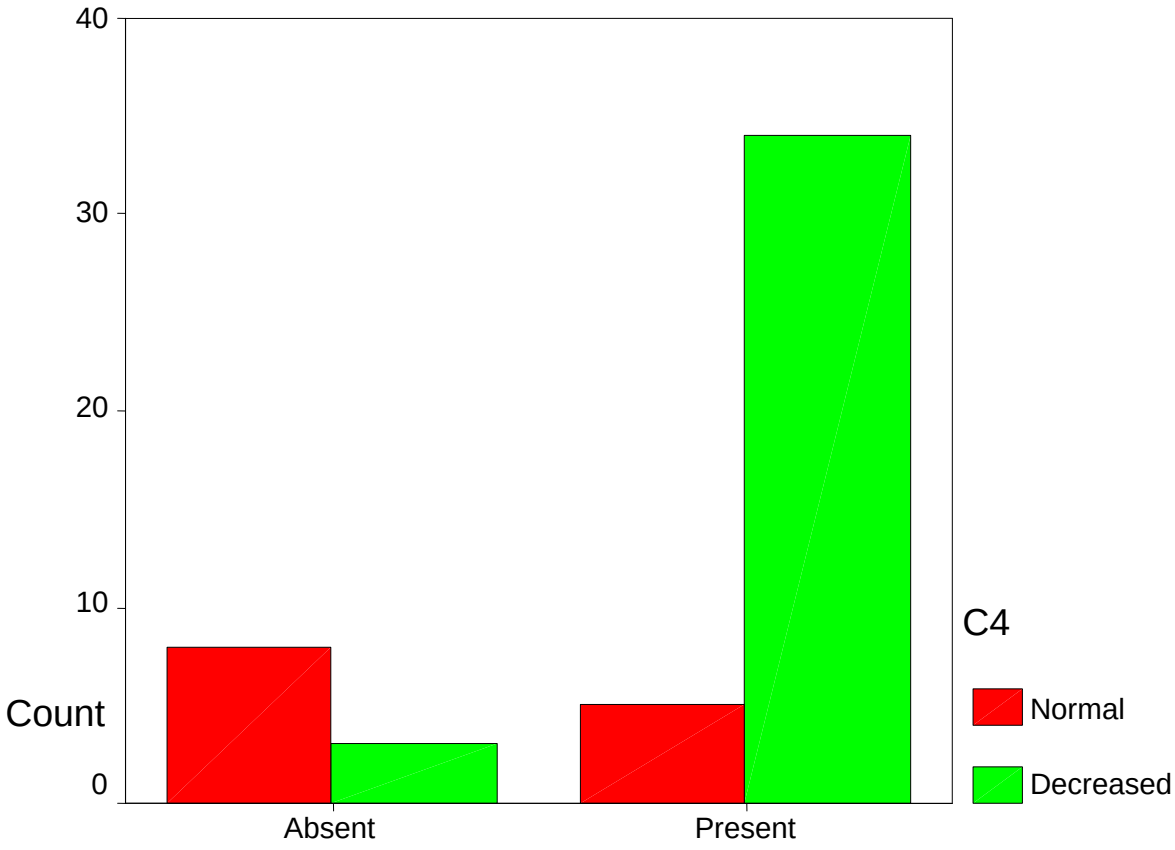
10
0
Count
II
IV
V
IV and V
Class of LN
C3
Normal
Decreased



Proliferative LN – Classes IV, IV&V


40
30
20
10
0
Count
II
IV
V
IV and V
Class of LN
C4
Normal
Decreased



Proliferative LN – Classes IV, IV&V

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A STUDY TO EVALUATE THE CORRELATION BETWEEN SEROLOGICAL PROFILE AND HISTOPATHOLOGY OF LUPUS NEPHRITIS INTRODUCTION: Systemic lupus erythematosus is an autoimmune disease of unknown etiology, characterized by the involvement of multiple organ systems 1. Organ damage is mediated by tissue binding autoantibodies and immune complexes. The hallmark of SLE is the presence of serum autoantibodies directed to nuclear constituents (i.e., antinuclear antibodies, ANA). In most of the patients, these autoantibodies are present for a few years before the first clinical symptoms appear 2. The clinical presentation and course of SLE are extremely variable. Some patients have spontaneous remissions; others...

A STUDY TO EVALUATE THE CORRELATION BETWEEN SEROLOGICAL PROFILE AND HISTOPATHOLOGY OF LUPUS NEPHRITIS

INTRODUCTION:

Systemic lupus erythematosus is an autoimmune disease of unknown etiology, characterized by the involvement of multiple organ systems [1]. Organ damage is mediated by tissue binding autoantibodies and immune complexes. The hallmark of SLE is the presence of serum autoantibodies directed to nuclear constituents (i.e., antinuclear antibodies, ANA). In most of the patients, these autoantibodies are present for a few years before the first clinical symptoms appear [2]. The clinical presentation and course of SLE are extremely variable. Some patients have spontaneous remissions; others may have mild musculoskeletal involvement which responds to therapy and a few die from progressive severe multisystem disease unresponsive to immunosuppressive therapy[2]. SLE commonly involves skin, joints, kidneys, serosal surfaces including pleura and pericardium, CNS and hematopoietic system.

Lupus nephritis is one of the common manifestations of SLE. Diagnosis of SLE is based on the 11 criteria defined by American Rheumatism Association (ARA). SLE patients develop wide range of autoantibodies [4,11,12,13]. ANA is the most sensitive test for SLE and is present in more than 90% of patients but not specific for SLE. Anti dsDNA is a more specific but less sensitive marker of SLE. High titre of anti dsDNA correlates with disease activity and especially with lupus nephritis[3, 4, 12, 14]. Serum levels of complements C3 and C4 are usually decreased in

PROFORMA

Name: **Age :** **Sex :**

Address: **Phone No:**

History:

Fever	Joint pain/swelling	Oral ulcer	Skin rash	Photosensitivity

Pedal edema	Facial puffiness	Frothy urine

Hypertension	Diabetes mellitus	Tuberculosis	Seizures

PIH	Abortion	IUD

General examination

Anemia: Yes / No

Malar rash: Yes / No

Jaundice: Yes/ No

Oral ulcer: Yes / No

Cyanosis: Yes / No

Arthritis: Yes / No

Clubbing: Yes / No

Purpuric spots: Yes / No

Lymphadenopathy: Yes / No

Pedal edema: Yes / No

Pulse rate:

BP:

Systemic examination

CVS:

Abdomen:

RS:

CNS:

Investigations:

1. Urine analysis:

Protein	Sugar	Deposits

2. Spot Urine PCR:

3. Urine Culture and Sensitivity:

4. Complete Blood Count:

Hb	TC	DC	Platelets	ESR

5. Peripheral smear:

6. Blood investigations:

Sugar	Urea	Creatinine

Bilirubin	SGOT	SGPT	ALP

Proteins

Total	Albumin	Globulin

7. Viral markers:

HIV	HBsAg	Anti HCV

8. Serological markers for SLE:

ANA	Anti dsDNA	C3	C4

9. ECG:

10. X-ray chest:

11. USG KUB:

12. Renal Biopsy:

Light microscopy	Immunofluorescence	Impression

13. Analysis of the study:

S.No	NAME	AGE	SEX	PROTEINURIA PCR > 0.5	MICROSCOPIC HEMATURIA	SERUM CREATININE	ANA	Anti ds DNA	C3	C4	RENAL BIOPSY ISN/RPS CLASS
1	AMUDHA	32	F	P	P	↑	POS	POS	↓	N	IV
2	GEETHA	20	F	P	P	N	POS	POS	↓	↓	IV
3	KALAIVANI	31	F	P	P	N	POS	POS	N	N	II
4	SELVI	27	F	P	P	N	POS	POS	↓	↓	IV & V
5	JAYANTHI	39	F	P	A	N	POS	NEG	N	N	II
6	ABINAYA SURIYA	15	F	P	P	N	POS	POS	↓	N	IV
7	GAYATHRI	21	F	P	P	N	POS	POS	↓	N	V
8	JAYA	35	F	P	A	N	POS	NEG	N	N	II
9	JAYANTHI	32	F	P	P	N	POS	NEG	N	N	II
10	SARITHA	22	F	P	P	↑	POS	POS	↓	↓	IV
11	SATHYA	23	F	P	P	N	POS	POS	↓	↓	IV
12	VALLIKANI	34	F	P	P	↑	POS	POS	↓	N	IV
13	SASI	18	F	P	P	↑	POS	POS	↓	N	IV
14	JOTHILAKSHMI	40	F	P	P	N	POS	POS	N	↓	V
15	VANITHA	37	F	P	P	N	POS	POS	N	N	IV
16	NASEEMA	45	F	P	P	↑	POS	POS	↓	↓	IV
17	REKHA	18	F	P	P	N	POS	POS	↓	↓	IV
18	SUMITHRA	27	F	P	A	N	POS	POS	↓	↓	IV
19	KASTHURI	21	F	P	P	N	POS	POS	↓	↓	IV
20	SELVI	40	F	P	A	N	POS	NEG	N	↓	V
21	PRABHAVATHI	25	F	P	P	↑	POS	POS	↓	↓	IV
22	PARIMALA	20	F	P	P	N	POS	POS	↓	↓	IV
23	SELVALAKSHMI	23	F	P	P	N	POS	POS	↓	↓	IV
24	REVATHI	31	F	P	A	N	POS	POS	↓	↓	IV
25	RAMAPRABHA	28	F	P	P	N	POS	POS	N	↓	IV
26	LATHA	33	F	P	P	N	POS	POS	N	↓	IV

27	RAMYA	16	F	P	P	N	POS	POS	↓	↓	IV
28	ANANTHI	28	F	P	P	N	POS	POS	↓	↓	IV
29	GNANASUNDARI	26	F	P	A	N	POS	NEG	N	N	II
30	SUDHA	29	F	P	A	N	POS	POS	↓	↓	IV & V
31	SASIKALA	24	F	P	A	↑	POS	POS	↓	↓	IV
32	MANICKAVALLI	17	F	P	P	N	POS	POS	↓	↓	IV & V
33	BANUMATHI	23	F	P	P	↑	POS	POS	↓	↓	IV
34	ANJALAI	38	F	P	P	↑	POS	POS	↓	↓	IV
35	ANITHA	25	F	P	A	N	POS	NEG	↓	↓	IV
36	BHAVANI	41	F	P	A	N	POS	NEG	N	N	II
37	HEMAMALINI	27	F	P	P	↑	POS	POS	↓	↓	IV
38	PUNITHAVALLI	32	F	P	P	↑	POS	POS	↓	↓	IV
39	YUVASRI	15	F	P	P	↑	POS	POS	↓	↓	IV
40	MEERA	15	F	P	P	↑	POS	POS	↓	↓	IV
41	GOKILA	28	F	P	P	N	POS	POS	N	↓	IV
42	KANIMOZHI	19	F	P	P	N	POS	POS	N	↓	IV
43	USHA	23	F	P	P	↑	POS	POS	↓	↓	IV
44	SUGANYA	19	F	P	A	N	POS	POS	↓	↓	IV
45	SARASWATHI	17	F	P	A	N	POS	NEG	N	N	II
46	VENMATHI	20	F	P	P	N	POS	POS	↓	↓	IV & V
47	BANGARAMMAL	35	F	P	P	↑	POS	POS	N	↓	IV
48	ANITHA	22	F	P	P	↑	POS	NEG	N	↓	V
49	PREETHA	15	F	P	A	N	POS	POS	↓	↓	IV
50	MARY ROSELINA	40	F	P	P	↑	POS	POS	↓	↓	IV

P - Present **A** - Absent
POS - Positive **NEG** - Negative
↑ - Increased ↓ -Decreased
N - Normal **F** - Female

INSTITUTIONAL ETHICAL COMMITTEE
GOVT.KILPAUK MEDICAL COLLEGE,CHENNAI-10
Ref.No.12054/EI(Ethics)/2011 Dt:03.01.2012
CERTIFICATE OF APPROVAL

The Institutional Ethical Committee of Govt. Kilpauk Medical College , Chennai reviewed and discussed the application for approval entitled "A study to evaluate the correlation between serological profile and histopathology of lupus nephritis" in patients attending a tertiary care Hospital in Chennai." submitted by Dr.C.Vasudevan, DM Nephrology, Post Graduate, Govt. Kilpauk Medical College, Chennai-10.

The Proposal is APPROVED.

The Institutional Ethical Committee expects to be informed about the progress of the study any Adverse Drug Reaction Occurring in the Course of the study any change in the protocol and patient information /informed consent and asks to be provided a copy of the final report.

GOVT. KILPAUK MEDICAL COLLEGE * Kilpauk, Chennai-10. *
26 OCT 2012

CHAIRMAN, 26/10/12
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Govt. Kilpauk Medical College,
Chennai